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10/586,555	10/08/2008	Yatendra Kumar	RLL-483US	6460

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Intellectual Property Department
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EXAMINER	
BALASUBRAMANIAN, VENKATARAMAN	
ART UNIT	PAPER NUMBER
1624	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/586,555	KUMAR ET AL.	
	Examiner	Art Unit	
	/Venkataraman Balasubramanian/	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/23/2006, 01/28/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-25 are pending.

Information Disclosure Statement

References cited in the Information Disclosure Statements, filed on 10/23/2006 & 01/28/2008, are made of record.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 5-7, 9 -11 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claim 5 is indefinite for more than on reason. Claim 5 refers to Formula II but there is no such formula in claim 5. Claim 5 includes a unlabeled formula with a R" group. But there is no definition of R" group and hence the structural make-up of this compound remains undefined. In addition, claim 5 shows two fragments, FORMULA A and FORMULA B. But there is no corresponding reference to these in the claim and hence purpose of showing these FORMULA A and FORMULA B is unclear. In addition, FORMULA B is a ketone fragment and it is not clear how such a group is converted to acid side chain of rosuvastatin.

2. Claim 6 is vague and unclear as it recites implicitly use of the amine slats as intermediates for making rosuvastatin or pharmaceutically acceptable salts, esters and lactones thereof. If it is a use claim, claim 6 provides for the use of amine salts of

rosuvastatin, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

3. Claim 7 is indefinite for more than on reason. Claim 7 refers to Formula IIa but there is no such formula in claim 7. Claim 7 includes a unlabeled formula with a R" group. But there is no definition of R" group and hence the structural make-up of this compound remains undefined. In addition, claim 7 shows two fragments, FORMULA A and FORMULA B. But there is no corresponding reference to these in the claim and hence purpose of showing these FORMULA A and FORMULA B is unclear. In addition, FORMULA B is a ketone fragment and it is not clear how such a group is converted to acid side chain of rosuvastatin.

4. Claim 9 is indefinite as it depends on claim 7 and claim 8. Hence, the scope of the claim is unclear. Note multiple dependency should be in alternate form.

5. Claim 10 is indefinite for more than on reason. Claim 10 refers to Formula IIb but there is no such formula in claim 10. Claim 10 includes a unlabeled formula with a R" group. But there is no definition of R" group and hence the structural make-up of this compound remains undefined. In addition, claim 10 shows two fragments, FORMULA A and FORMULA B. But there is no corresponding reference to these in the claim and hence purpose of showing these FORMULA A and FORMULA B is unclear. In addition, FORMULA B is a ketone fragment and it is not clear how such a group is converted to acid side chain of rosuvastatin.

6. Claim 24 is indefinite as it recites "amine salts of...". Markush choice should be alternate form. As recited the composition includes all amine salts of formula I and it is not clear that is what intended.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12, 24 and 25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making amine salts of rosuvastatin of formula I, does not reasonably provide enablement for making solvate, hydrate or crystalline or amorphous forms thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The following apply.

In evaluating the enablement question, several factors are to be considered. Note In re Wands, 8 USPQ2d 1400 and Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1. The nature of the invention and the state of the prior art:

The invention is drawn to amine salt of rosuvastatin of formula I, or a pharmaceutically acceptable salt, solvate, hydrate, crystal or amorphous form thereof. Specification is not adequately enabled as to how to make hydrate of compounds of

formula (I) Specification has no example of solvate of the instant compounds. Specification recites solvate thereof but there is no enabling of such compounds.

The compound of formula I embrace rosuvastatin salts with amines with variable groups, R_1, R_2, and R_3. Even a cursory calculation of the number of compounds embraced in the instant formula (I) based on the generic definition of optionally substituted alkyl, aryl, cycloalkyl, heteroaryl, heterocyclyl, heteroarylalkyl, arylalkyl, and etc would result in large number of compounds. This is of course not the accurate number and the true number of compounds would far exceed million compounds. Thus the genus embraced in the claim 1 is too large and there is no teaching of any solvate or hydrate or polymorph of this large genus.

Search in the pertinent art, including water as solvent resulted in a pertinent reference, which is indicative of unpredictability of hydrate formation in general. The state of the art is that is not predictable whether solvates or hydrates will form or what their composition will be. In the language of the physical chemist, a hydrate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is the compositional extent". Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometery of the formed solvate, i.e. if one, two, or a half a molecule of solvent

added per molecule of host. Compared with polymorphs, there is an additional degree of freedom to hydrates, which means a different solvent or even the moisture of the air that might change the stabile region of the hydrate. In the instant case of hydrate a similar reasoning therefore applies. Water is a solvent and hence it is held that a pertinent detail of West, which relates to solvates, is also applicable to hydrate. Specification has no working example of solvate or polymorph of compound of formula (I); Further, the specification does not provide any explanation of what types of 'polymorphs' are intended, how these are made, etc. The existence, structure and the properties (e.g., stability, solubility, bioavilability, rate of dissolution, etc.) of polymorphs tend to be very unpredictable. In order to establish the most stable polymorphic form, each has to be characterized and screened individually using various analytical techniques such as X-ray diffraction, thermal analysis, particle morphology characterization, etc. In view of the lack of direction provided in the specification regarding the starting materials, the lack of working examples and the general unpredictability of chemical reactions, it would take an undue amount of experimentation for one skilled in the art to make the claimed compounds and therefore practice the invention. The starting material sources necessary to obtain the instant compounds must have been available as of the filing date in order to provide an enabling disclosure. See In re Howarth, 654 F.2d 103,210 USPQ 689 (CCPA 1981); Exparte Moersch, 104 USPQ 122 (POBA 1954). Specification is not adequately enabled as to how to make solvate of compounds of formula (I). Specification neither discloses what types of solvates are intended nor has any examples of solvates of the

instant compounds. Specification on page 19 recites solvates but there is no enabling disclosure of such solvates or hydrates. The compound of formula I embrace rosuvastatin compounds forming salts with various amines with variable groups R1, R2, R3, which further optionally substituted. Careful calculation of the number of compounds embraced in the instant formula (I) shows a large number of compounds. Thus, the genus encompassed by the claims is excessively large and there is no teaching of any solvate or polymorph of this large genus. Search in the pertinent art, including water as solvent resulted in a pertinent reference, which is indicative of unpredictability of solvate formation in general.

In addition, an additional search resulted in Vippagunta et al., Advanced Drug Delivery Reviews 48: 3-26, 2001, which clearly states that formation of hydrates in unpredictable. See entire document especially page 18, right column section 3.4. Note Vippagunta et al., states "Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for series of related compounds". Regarding polymorphs, the reference provides that "The main challenge in managing the phenomenon of multiple solid forms of a drug is the inability to predict the number of forms that can be expected in a given case. This prediction would involve quantification of the myriad intermolecular forces within any proposed crystal structure as well as the ability to postulate the likely packing modes for a given molecule in all its configurations" (see page 11, col. 2).

Joachim Ulrich (Kirk-Othmer Encyclopedia of Chemical Technology) provides that "Pseudopolymorphs are solvates or in the case of water as solvent, hydrates, which

means crystals that incorporate solvent molecules into the crystal lattice. Pseudopolymorphs exhibit different crystal forms and/or different densities, solubilities, dissolution rates, colors, hardnesses, etc. Compared with polymorphs, there is an additional degree of freedom (than temperature and pressure), which means a different solvent or even the moisture of the air that might change the stabile region of the pseudopolymorph".

Also, note MPEP 2164.08(b) which states that claims that read on "... significant numbers of inoperative embodiments would render claims nonenabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative.". Clearly that is the case here.

2. The predictability or lack thereof in the art:

Hence, the solvate as applied to the above-mentioned compounds claimed by the applicant are not art-recognized compounds and hence there should be adequate enabling disclosure in the specification with working example(s).

3. The amount of direction or guidance present:

Examples illustrated in the experimental section are limited to making the compounds not related to solvates. There is no example of a solvate of instant compound. Five compounds were shown in the examples of the specification each of which has come in contact with water and other solvent but there is no showing that instant compounds formed solvates or hydrates or polymorphs. Hence it is clear that merely bring the compound with solvent or water does not result in solvate or hydrate

and additional direction or guidance is needed to make them Specication has no such direction or guidance.

4. The presence or absence of working examples:

There is no working example of any solvate or hydrate or polymorph formed. The claims are drawn to hydrate, yet the numerous examples presented all failed to produce a solvate or hydrate or polymorph. These cannot be simply willed into existence. As was stated in Morton International Inc. v. Cardinal Chemical Co., 28 USPQ2d 1190 "The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there, is no evidence that such compounds exist... the examples of the '881 patent do not produce the postulated compounds... there is ...' no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that hydrates of these compounds actually exists; if they did, they would have formed. Hence, there should be showing supporting that solvates and hydrates of these compounds exist and therefore can be made.

5. The breadth of the claims & the quantity of experimentation needed:

Specication has no support, as noted above, for compounds generically embraced in the claims 1-12, 24 and 26 would lead to desired solvate, hydrate or polymorph of the compound of formula I. As noted above, the genus embraces large number of compounds and hence the breadth of the claim is broad. The quantity of experimentation needed would be an undue burden on skilled art in the chemical art since there is inadequate guidance given to the skilled artisan for the many reasons

stated above. Even with the undue burden of experimentation, there is no guarantee that one would get the product of desired solvate of compound of formula I embraced in the instant claims in view of the pertinent reference teachings.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

MPEP 2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here. Thus, undue experimentation will be required to make Applicants' invention.

Claim 25 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for hypercholesteromia does not reasonably provide enablement for the treatment of disease conditions disorders wherein HMG-CoA is implicated as generically embraced. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note In re Wands, 8 USPQ2d 1400 and Ex parte Forman, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

1) The nature of the invention: The instant method of use claim 25 is drawn to treating disease conditions wherein HMG-CoA implicated using amine salt of rosuvastatin and thereby treating any or all disorders based on the mode of action of instant compounds as HMG -CoA reductase inhibitors in general.

Instant claim 25, as recited, is a reach through claim. A reach through claim is a claim drawn to a mechanistic, receptor binding or enzymatic functionality in general format and thereby reach through a scope of invention for which they lack adequate written description and enabling disclosure in the specification.

In the instant case, based on the inhibition of HMG CoA reductase by the instant compounds, instant claim reaches through inhibiting and treating any or all disorders in general and thereby they lack adequate written description and enabling disclosure in the specification.

More specifically, in the instant case, based on the mode of action of instant compounds as inhibition of HMG CoA reductase, based on limited assay, it is claimed that treating any or all disorders in general, which is not adequately enabled solely based on the activity of the compounds provided in the specification. The instant

compounds are disclosed to have HMG CoA reductase inhibitory activity and it is recited that the instant compounds are therefore useful in treating any or all diseases stated above for which applicants provide no competent evidence. It appears that the applicants are asserting that the embraced compounds because of their mode action as HMG CoA reductase inhibitor would be useful for all sorts of diseases including cancers. However, the applicants have not provided any competent evidence that the instantly disclosed tests are highly predictive for all the uses disclosed and embraced by the claim language for the intended host.

No compound has ever been found to treat all types of medical conditions or diseases generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "compound" is contrary to our present understanding of modern medicine.

Note substantiation of utility and its scope is required when utility is "speculative", "sufficiently unusual" or not provided. See Ex parte Jovanovics, 211 USPQ 907, 909; In re Langer 183 USPQ 288. Also note Hoffman v. Klaus 9 USPQ 2d 1657 and Ex parte Powers 220 USPQ 925 regarding type of testing needed to support in vivo uses.

Next, applicant's attention is drawn to the Revised Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001 wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed method treating solely based on the inhibitory activity disclosed for the compounds. The state of the art at the time of instant

invention is indicative of the requirement for undue experimentation. See Khan et al., Diabetes Care 25(4), 708-771, 2002, Iida et al., FEBS Letters 520, 177-181, 2002 and Rutishauser Swiss Medical Weekly, 126, 41-49, 2006.

The method of use claims are drawn to treating of variety of diseases and disorders. However, specification provides no support for treating all or any diseases/disorders. In fact, based on the specification and examples, it appears that the instant compounds are mainly HMG CoA reductase inhibitors and may be useful for treating hypercholesterolemia. Specification has not provided any evidence or nexus that because of the mode of action of the instant compound, the compound would be useful for treating any or all said diseases/disorders. Such a reasonable correlation is necessary to demonstrate such utilities. See Ex parte Stevens, 16 USPQ 2d 1379 (BPAI 1990); Ex parte Busse et al., 1 USPQ 2d 1908 (BPAI 1986) (the evidence must be accepted as "showing" such utility, and not "warranting further study"). The evidence presented in this case does not show such utilities related to all disorders, but only warrants further study.

2) The state of the prior art:

Recent publications expressed that the inhibition effects of HMG CoA reductase are unpredictable and are still exploratory. See Khan et al., Iida et al., and Rutishauser cited above.

3) The predictability or lack thereof in the art:

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use for treating all the said diseases and

disorders by the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

4) The amount of direction or guidance present and 5) the presence or absence of working examples:

Specification has no working examples to show treating and any or all diseases recited in the instant claims and the state of the art is that the effects of HMG CoA reductase inhibitors are unpredictable.

6) The breadth of the claims:

The instant claims embrace treating various diseases with huge genus of compounds.

7) The quantity of experimentation:

The quantity of experimentation needed would be an undue burden to one skilled in the pharmaceutical arts since there is inadequate guidance given to the skilled artisan, regarding the pharmaceutical use, for the reasons stated above.

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the instant case for the instant method claims. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of enzyme-inhibitor interactions in general, and the lack of working examples regarding the activity of the claimed compounds

towards treating the variety of diseases of the instant claims, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate in scope with the claims.

Note MPEP 2164.08(b) which states that claims that read on "... significant numbers of inoperative embodiments would render claims nonenabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative.". Clearly that is the case here.

Also note, Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was 'filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)." That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claim 6 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-9, 13, 14, 18, 19, 24 and 25 are rejected under 35 U.S.C. 102(e) as being anticipated by Niddam-Hildesheim et al., US 20050131066, now US 7,777,034.

Niddam-Hildesheim teaches crystalline ammonium salts of rosuvastatin and their X-ray diffraction pattern and their use for making rosuvastatin calcium. See entire document. See pages 2-6 for details of the invention, process of making, composition and method of use. Especially see examples 1-5 for various crystalline ammonium salts, process of making them and their use for making rosuvastatin calcium.

Instant specification has no showing that these amine salts of rosuvastatin taught by Niddam-Hildesheim are different from corresponding instant compounds.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-9, 13, 14, 18, 19, 24 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Niddam-Hildesheim et al., US 20050131066, now US 7,777,034.

Niddam-Hildesheim teaches crystalline ammonium salts of rosuvastatin and their X-ray diffraction pattern and their use for making rosuvastatin calcium. See entire document. See pages 2-6 for details of the invention, process of making, composition and method of use. Especially see examples 1-5 for various crystalline ammonium salts, process of making them and their use for making rosuvastatin calcium.

Instant specification has no showing that these amine salts of rosuvastatin taught by Niddam-Hildesheim are different from corresponding instant compounds.

Instant claims require in addition to the primary amine salts discussed above, secondary amine salts as well.

While said compounds do not anticipate the scope of instant claims when the amine is secondary such as N-methyl-isopropyl amine or N-methyl-cyclohexylamine as generically claimed in the instant claims, they are very closely related having NH_2 in the reference versus $NHCH_3$ in the instant claims. However, compounds that differ only in having H vs Me on nitrogen are not deemed patentably distinct absent evidence of superior or unexpected properties. See for compounds that differ only as H vs Me on nitrogen, Ex parte Weston 121 USPQ 428; In re Doebel 174 USPQ 156.

Similarly, instant claims include generically propylamine and butylamine, cyclopentyl amine and cycloheptylamine and methyl-cyclopentylamine. Instant compounds require a carboxyl group at 2 or 4 position for R_1 and an amino at other available position for R_2.

While said compound(s) doesn't anticipate the scope of instant claims, they are very closely related, being positional isomers of compounds i.e. isopropyl in the reference amine versus n-propyl in the instant amine. However, positional isomers are not deemed patentably distinct absent evidence of superior or unexpected properties. See In re Crounse, 150 USPQ 554; In re Norris 84 USPQ 458; In re Finely 81 USPQ 383 and 387; Ex parte Engelhardt, 208 USPQ 343; Ex parte Henkel, 130 USPQ 474, regarding positional isomers.

In addition, instant claims include generically butylamine, cyclopentyl amine and cycloheptylamine as amines for salt formation with rosuvastatin. While said compound

doesn't anticipate the scope of instant claims, they are very closely related, being homolog that is compounds that differ in butyl in the reference on vs. propyl as well as cyclopentyl or cycloheptyl in the amine of the reference versus cyclohexyl in the instant amine. However, homologs and compounds that differ only by CH3 Vs H are not deemed patentably distinct absent evidence of superior or unexpected properties. See In re Wood 199 USPQ 137; In re Lohr 137 USPQ 548.

Thus, one skilled in the art at the time of the invention would have been motivated to make compounds that have methyl on the nitrogen and expect the these compounds to possess the utility in the instant case in view of the close structural similarity outlined above.

Claims 1-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Taylor et al., WO 01/60804 in view of Pflaum et al., WO 00/17150 and Lim et al. WO 03/087112.

1. Determining the scope and contents of the prior art:

The claimed invention relates to various amine salts of rosuvastatin and a process of preparing amine salts of rosuvastatin by treating rosuvastatin with various amines.

The amine salts of rosuvastatin and the overall process of making an amine salt of rosuvastatin is well known in the art.

Taylor et al., teaches several crystalline ammonium salts of rosuvastatin, the process of making them, their X-ray diffraction pattern and their use in making rosuvastatin calcium. See entire document. See pages 1-3 for details of the invention,

various amine salts and X-ray diffraction. See also figures 1-7. Especially see pages 3-6, examples 1-10 for various crystalline ammonium salts and rosuvastatin calcium salt prepared from amine salts.

2. Ascertaining the differences between the prior art and the claims at issue:

The claimed invention requires use of primary amine, secondary amine and tertiary amine as embraced in the generic formula $NR_1R_2R_3$ for making the amine salts and the proviso in the claims excludes specific amine salts taught by Taylor.

3. Resolving the level of ordinary skill in the pertinent art:

While said compounds do not anticipate the scope of instant claims when the amine is secondary such as N-methyl-isopropyl amine or N-methyl-cyclohexylamine as generically claimed in the instant claims, they are very closely related having NH_2 in the reference versus $NHCH_3$ in the instant claims. However, compounds that differ only in having H vs Me on nitrogen are not deemed patentably distinct absent evidence of superior or unexpected properties. See for compounds that differ only as H vs Me on nitrogen, Ex parte Weston 121 USPQ 428; In re Doebel 174 USPQ 156.

Similarly, instant claims include generically propylamine and butylamine, cyclopentylamine and cycloheptylamine and methyl-cyclopentylamine. Instant compounds require a carboxyl group at 2 or 4 positions for R_1 and an amino at other available position for R_2.

While said compound(s) doesn't anticipate the scope of instant claims, they are very closely related, being positional isomers of compounds i.e. isopropyl in the reference amine versus n-propyl in the instant amine. However, positional isomers are

not deemed patentably distinct absent evidence of superior or unexpected properties. See In re Crounse, 150 USPQ 554; In re Norris 84 USPQ 458; In re Finely 81 USPQ 383 and 387; Ex parte Engelhardt, 208 USPQ 343; Ex parte Henkel, 130 USPQ 474, regarding positional isomers.

In addition, instant claims include generically butylamine, cyclopentyl amine and cycloheptylamine as amines for salt formation with rosuvastatin. While said compound doesn't anticipate the scope of instant claims, they are very closely related, being homolog that is compounds that differ in butyl in the reference on vs. propyl as well as cyclopentyl or cycloheptyl in the amine of the reference versus cyclohexyl in the instant amine. However, homologs and compounds that differ only by CH3 Vs H are not deemed patentably distinct absent evidence of superior or unexpected properties. See In re Wood 199 USPQ 137; In re Lohr 137 USPQ 548.

Thus it would have been obvious to one skilled in the art at the time of the invention was made to expect instant compounds to possess the utility taught by the applied art in view of the close structural similarity outlined above.

Furthermore, the secondary reference Pflaum teaches that ammonium salts from various amines including secondary amines for making salts of statins in general. See entire document, especially page 8, entry b which includes isopropyl amine as well. Note the ammonium salt formation is with the carboxylate group of these statins and is same as the salt formation with rosuvastatin.

In addition, the second secondary reference Lim teaches equivalency various statins. See pages 1-20.

Thus, one trained in the art would be motivated to makes ammoniums salts of rosuvastain based on the combined teachings of primary and secondary references including isopropyl salt of the rosuvastain in view of the generic teaching of the secondary reference and the specific benefits of such salt taught in the primary reference.

Also see KSR International Co. v. Teleflex Inc., 127 S.Ct. 1727 (2007), wherein the court stated that

[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

Such is the case with instant claims. Taylor teaches organic amines for forming salt of rosuvastatin and the homologs, positional isomers and NH versus $NH\text{-}CH_3$ compounds of these amines are obvious over the amines of instant claims as stated above. In addition, the secondary reference Pflaum also teaches a variety of amines can be used for making crystalline salts of statins. Lim teaches equivalency of statins including in the side chain lactone and free carboxylic acid portion. Given such a general teaching and the art of salt formation is well known, it would be obvious to one trained in the art to make various amine salts of rosuvastatin. Hence, based on these teaching one trained in the art would be motivated to make ammonium salts of rosuvastatin using various amines based on the guidance provided by the combined

teaching of these references. Such amine salts are within the skill set of one trained in the art.

Hence, based on the above factual analysis and the relevant case laws cited, this rejection is proper. Besides the case laws cited above, there are several case laws, which support the same notion. These are discussed below:

Compounds that differ only by the presence or absence of an extra methyl group or two are homologues. Homologues are of such close structural similarity that the disclosure of a compound renders prima facie obvious its homologue. As was stated in In re Grose, 201 USPQ 57, 63, "The known structural relationship between adjacent homologues, for example, supplies a chemical theory upon which a prima facie case of obviousness of a compound may rest." The homologue is expected to be preparable by the same method and to have generally the same properties. This expectation is then deemed the motivation for preparing homologues. Of course, these presumptions are rebuttable by the showing of unexpected effects, but initially, the homologues are obvious even in the absence of a specific teaching to add or remove methyl groups. See In re Wood, 199 USPQ 137; In re Hoke, 195 USPQ 148; In re Lohr, 137 USPQ 548; In re Magerlein, 202 USPQ 473; In re Wiechert, 152 USPQ 247; Ex parte Henkel, 130 USPQ 474; In re Jones, 74 USPQ 152, 154; In re Herr, 134 USPQ 176; Exparte Dibella, 157 USPQ 59; In re Zickendraht, 138 USPQ 22; Ex Parte Fischer, 96 USPQ 345; In re Fauque, 121 USPQ 425; In re Druey, 138 USPQ 39; In re Bowers and Orr, 149 USPQ 570. In all of these cases, the close structural similarity between two compounds differing by one or two methyl groups was itself sufficient show

obviousness. As was stated directly in THE GENERAL TIRE & RUBBER COMPANY v. JEFFERSON CHEMICAL COMPANY, INC., 182 USPQ 70 (1974): "If any structural change is obvious to one skilled in the art, a substitution of the next higher homolog would seem to be." Note also In re Jones, 21 USPQ2d 1942, which states at 1943 "Particular types or categories of structural similarity without more, have, in past cases, given rise to prima facie obviousness"; one of those listed is "adjacent homologues and structural isomers". Similar is In re Schechter and LaForge, 98 USPQ 144, 150, which states "a novel useful chemical compound which is homologous or isomeric with compounds of the prior art is unpatentable unless it possesses some unobvious or unexpected beneficial property not possessed by the prior art compounds." Note also In re Deue134 USPQ2d 1210, 1214 which states, "Structural relationships may provide the requisite motivation or suggestion to modify known compounds to obtain new compounds. For example, a prior art compound may suggest its homologs because homologs often have similar properties and therefore chemists of ordinary skill would ordinarily contemplate making them to try to obtain compounds with improved properties." See also MPEP 2144.09, second paragraph.

Hence, again, based on the above factual analysis and the relevant case laws cited, this rejection is proper.

4. Considering objective evidence present in the application indicating obviousness or nonobviousness:

Specification has no comparative data to showing any unexpected superior results. Hence, the claimed invention is an obvious variant of prior art amine salts and process cited above.

Conclusion

Any inquiry concerning this communication from the examiner should be addressed to Venkataraman Balasubramanian (Bala) whose telephone number is (571) 272-0662. The examiner can normally be reached on Monday through Thursday from 8.00 AM to 6.00 PM. The Supervisory Patent Examiner (SPE) of the art unit 1624 is James O. Wilson, whose telephone number is 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

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/Venkataraman Balasubramanian/

Primary Examiner, Art Unit 1624